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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,315	08/10/2001	Charles S. Zuker	02307E-120110US	4699

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EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,315	ZUKER ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,49-51,56-58,69-72,75 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,49-51,56-58,69-72,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Status of Application: Claims and Amendments

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/01/05 has been entered.

Applicant is notified that the amendments put forth on 08/01/05 have been entered in full.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

Maintained Rejections:

Claims 49-51, 56-58, 69, 71, 72, 75, 76 are rejected under 35 U.S.C. 112, second paragraph, as set forth previously regarding claims 49-51 and 55-78, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reason.

Claims 49-51, 56-58, 69, 71, 72, 75, 76 require a "functional effect", although the specification recites several examples of "functional effects" the skilled artisan could not be sure whether or not he or she was practicing the claimed invention because of the presence of such an ambiguous term.

Applicant argues that the examples provided in the specification provide sufficient detail to allow the metes and bounds of the claims to be determined. This argument has been fully considered but not deemed persuasive. Examples cannot define the bounds of a concept; and the claims are not limited to those examples, thus the bounds of the claims are subject to the interpretation of the individual and are thus indefinite.

Applicant argues that the prior art teaches numerous examples of functional effects of GPCRs. This argument has been fully considered but not deemed persuasive. While many different functional effects are known for the family of GPCRs, the instant specification has not set forth what functional effects are considered to relate specifically to the instant T1R3/T1R2 complex. Specific definitions as they relate to the T1R3/T1R2 complex are needed, not generalized definitions of functional effects that do not relate to any single GPCR family member.

Furthermore, it is inaccurate to imply that because T1R3 and T1R2 are GPCRs they are thus members of a well characterized family. T1R3 and T1R3 are members of an odd subgroup of GPCRs, termed Class C or Class III GPCRs, characterized by an extremely long N-terminal ligand binding domain, and further distinguished by the fact that they function as hetero or homodimers. Reviewing this group, Hermans and Challiss write "Currently available data suggest that family C GPCRs share a number of structural, biochemical and regulatory characteristics which differ markedly from those of the other GPCR families, most notably the rhodopsin/family A GPCRs that have been most widely studied to date", see the Abstract of Hermans-E., et al., Biochem. J. 359(465)2001.

Claims 49-51, 56-58, 67, 69-72, 75, 76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying activators and inhibitors of sweet taste signal transduction, comprising a taste cell receptor composed of a heterodimer of SEQ ID NO: 9 and 15, wherein the receptor is present on the surface of a cell, and wherein the receptor is coupled to a Gα15 or Gα16 protein, does not reasonably provide enablement for methods employing artificially constructed variants of SEQ ID NO: 9 and 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A) The claims encompass the use polypeptide variants of the polypeptides of SEQ ID NO: 9 and 15 (substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 9 or 15) i.e. protein variants encoded polynucleotides that need only hybridize to a polynucleotide encoding SEQ ID NO: 9 and 15. Although the specification indicates that such variants are encompassed by the invention (e.g. page 5), no specific teaching is provided to indicate which amino acid substitutions, deletions or insertions to make. The specification has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 9 or 15, but which still retain a desired property of the polypeptide of SEQ ID NO: 9 or 15. Furthermore, the specification has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 9 or 15 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not

defined a difference in structure or difference in function between the proteins corresponding to SEQ ID NO: 9 and 15 and variants of said proteins. If a variant of a protein corresponding to SEQ ID NO: 9 or 15 is to have a structure and function similar to a protein corresponding to SEQ ID NO: 9 or 15, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of a protein corresponding to SEQ ID NO: 9 or 15. Conversely, if a protein variant of SEQ ID NO: 9 or 15 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification provides the suggestion that such variants can be obtained, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses those naturally occurring compositions known to the inventor, i.e. SEQ ID NO: 9 and 15. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). With regard to enablement for artificially constructed variants of the polypeptides of SEQ ID NO: 9 and 15, the instant fact pattern is actually one step removed and deficient from that of *Hyatt*. The instant specification does not disclose any working examples of artificially constructed variants of the polypeptides encoded by SEQ ID NO: 9 and 15.

Applicant has argued that given the advanced state of molecular biology an artisan could easily make a functional variant that is 90% identical to SEQ ID NO: 9 or 15 and that it is routine in the field to do so by avoiding areas of conservation between related sequences. This argument has been fully considered but not deemed persuasive. First, the claims are to a genus not to a single variant, such a genus not being supported by the specification. Regarding the advanced state of the art, Applicant is referred to Guo et al. PNAS 101(9205-9210)2004 wherein the authors completed a systematic study of the tolerance that natural proteins have to amino acid sequence change. They found that on average a single amino acid replacement had a 34% chance of inactivating a protein, see the Abstract. The instant SEQ ID NO: 9 and 15 are disclosed as consisting of 838 and 858 amino acids respectively. A polypeptide 90% identical to SEQ ID NO: 9 or 15 would have as many as 83 or 85 amino acid substitutions relative to SEQ ID NO: 9 and 15. Thus, the expectation that any given artificially synthesized polypeptide that is 90% identical to SEQ ID NO: 9 or 15 would be functional is astronomically low.

Applicant argues Guo et al. make random mutations, and that the skilled artisan would makereasoned changes, e.g. conservative changes and in regions that are less likely to be detrimental to the functioning of the receptor. This argument has been fully considered but not deemed persuasive. Applicant is again referred to Bowie et al. at page 1308, col 1, last paragraph. Bowie teaches "Functionally important residues should be conserved in sets of active sequences, bit it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved. To make this distinction requires an independent assay of protein folding". Thus, with nothing but sequence data provided in the

specification, the Artisan is left to essentially random trial and error experimentation to try to find positions which are tolerant to change.

No evidence has been put fourth to support Applicant's argument or refute the teachings of Bowie et al. referred to above and the analysis made in the rejection. Arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964).

Applicant has argued that an exhaustive teaching of all possible modifications of an exemplary T1R2 or T1R3 is a practical impossibility. This argument has been fully considered but not deemed persuasive. No such exhaustive listing has been required. Rather, the specification, which has failed to disclose even a single modification, has failed to provide an enabling disclosure for the claimed genus.

(C) The specification puts forth that the sweet receptor can be coupled to a G-protein or a promiscuous Gα15 G-protein (see page12, line 23), however the only particular G-protein that is taught to work in the claimed invention is Gα15, although the promiscuous G-protein Gα16 would be expected to as well. The claims encompass, and the specification contemplates, using other G-proteins. The claims encompass the use of the endogenous G-protein(s) and the skilled artisan appreciates that such a use would be desirable, yet the specification has not provided any, and nor is such known in the prior art. Essentially, therefore, the specification has merely invited the skilled artisan to embark on an extensive research plan to try to find other G-proteins that would work in the invention. Such a call for extensive trial and error experimentation places an

undue burden on the skilled artisan trying to practice the invention commensurate with the scope of what is being claimed. Additionally, in this regard the claims are also single means claims, because the claims encompass any method having the recited activities whereas the instant specification only discloses the single method known to the inventor.

Applicants specific arguments are addressed below.

The Breadth of the claims

Applicant argues that the claims require structural and functional limitations that limit the scope. This argument has been fully considered but not deemed persuasive. The claims require an encompass an essentially limitless number of polypeptide variants of SEQ ID NO: 9 and 15. One skilled in the art appreciates that the recitation of percent identity describes no particular sequence, and that simply verbalizing or writing down that such an undescribed sequence should have a particular activity in no way enables one to make such a sequence.

The Nature of the invention

Applicant argues that the discovery of the instant invention is pioneering. The examiner agrees, yet the pioneering nature of the invention tends to limit rather than enhance the teachings of the prior art that Applicant relies on to fill gaps in the teachings of the instant specification.

The State of the Prior Art

Applicant argues that the prior art regarding GPCRs is well developed and that the molecular properties of GPCRs are well understood. This argument has been fully considered but not deemed persuasive. As set forth above, it is inaccurate to imply that because T1R3 and T1R2 are GPCRs they are thus members of a well characterized family. T1R3 and T1R3 are members of an odd subgroup of GPCRs, termed Class C or Class III GPCRs, characterized by an

extremely long N-terminal ligand binding domain, and further distinguished by the fact that they function as hetero or homodimers. Reviewing this group, Hermans and Challiss write "Currently available data suggest that family C GPCRs share a number of structural, biochemical and regulatory characteristics which differ markedly from those of the other GPCR families, most notably the rhodopsin/family A GPCRs that have been most widely studied to date", see the Abstract of Hermans-E., et al., Biochem. J. 359(465)2001.

The level of one of ordinary skill

The examiner agrees that the level of skill is quite high, yet the examiner is aware of no instance in the reported literature wherein the ordinary artisan has produced a genus of functional GPCRs (of any class) that would be representative of the genus required of the claims.

The level of predictability in the art

As set forth above, Applicant argues Guo et al. make random mutations, and that the skilled artisan would make reasoned changes, e.g. conservative changes and in regions that are less likely to be detrimental to the functioning of the receptor. This argument has been fully considered but not deemed persuasive. Applicant is again referred to Bowie et al. at page 1308, col 1, last paragraph. Bowie teaches "Functionally important residues should be conserved in sets of active sequences, bit it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved. To make this distinction requires an independent assay of protein folding". Thus, with nothing but sequence data provided in the specification, the Artisan is left to essentially random trial and error experimentation to try to find positions which are tolerant to change.

The amount of direction provided by the inventor

Applicant's arguments regarding sequence data have been addressed directly above. Furthermore, Applicant argues that the instant fact pattern is distinguished from *In re Hyatt* and *Fiers v. Sugano*, in that actual sequences are disclosed. This argument has been fully considered but not deemed persuasive. The claims encompass a vast genus of naturally and artificially constructed polypeptides. No artificially constructed sequences have been disclosed. As set for above, the recitation of percent identity discloses no other sequence than the reference SEQ ID NO.

The existence of working examples

No examples of what is essentially the largest portion of the genus, i.e., artificially constructed sequences, have been disclosed.

Quantity of experimentation needed

Applicant arguments have been addressed under the headings The level of predictability in the art and The level of one of ordinary skill, above.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under

37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

September 12, 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER